REMARKS

1. Allowable Subject Matter; Claim Amendments

1.1. The examiner concedes that the subject matter of claims 14, 18, 19, 36, and 37 would be allowable if those claims were rewritten in independent form.

Claim 14: at least one of the two peptide sequences is SEQ ID NO:2.

Claim 18: "fragment" of compound consists of SEQ ID NO:2.

Claim 19: compound comprises both SEQ ID NO:1 and SEQ ID NO:2.

Claim 36: both sequences are SEQ ID NO:2.

Claim 37: similar to claim 19.

1.2. Claims 4-10, 15-16, 37-38 and 40-49 have been cancelled and claims 1, 11, 17-20, and 35-36 amended.

Claim 1 has been amended to recite

(1) each of the individual peptide sequences is 6-20 AA in length, and

(2) at least one individual peptide sequence is SEQ ID NO:1 or 2, or a fragment of at least 40% the length thereof.

Formula (I) has been deleted as moot in view of point (2) above.

Basis for claim 1 amendments is

6-10 Aa: P19, L30

40% length: P33, L7-11.

We note that SEQ ID NO:1 is 15 amino acids in length, whereas SEQ ID NO:2 is 16 amino acids long. Hence, the "fragments thereof having at least 40% of the length of said sequences" must be at least 6 amino acids long in the case of SEQ ID NO:1 and at least 7 amino acids long in the case of SEQ ID NO:2. There is independent support for these minimum lengths at P18, L25-P21, L2.

Claim 39, with basis at P20, L8-11 and P20, L35-P21, L2,

requires that the sequence "comprises at least 9 consecutive amino acids of SEQ ID NO:1 or SEQ ID NO:2".

In view of the amendments of claim 1, the distinction between 19 and 37 was obliterated, and hence 37 has been cancelled as a duplicate claim.

2. Formal Matters

2.1. Election/Restriction

The Examiner was not satisfied that the 69 sequences cited in claim 11 are unified, in part due to the fact that they are derived from different proteins. SEQ ID NOs 1 and 2 were both elected, and both are derived from NCAM (as also discussed by the Examiner; OA page 2).

The claims have been amended to require the presence of SEQ ID NO:1 or 2, or a fragment thereof.

2.2. Abstract

The Examiner contends that the abstract does not conform to the requirements (page 6 of OA). The original abstract is 106 words long, and thus not too long (50-150 words being deemed acceptable). The Examiner has not specified how the abstract is faulty. We have nonetheless rewritten the abstract in the hope of satisfying the examiner.

2.3. Sequence listing and sequences in specification (OA §7)

The Examiner questions the reference to SEQ ID NO:147 in the text when the filed sequence listing contains only 146 sequences.

The sequence listing submitted with the USPTO on February 7, 2006 contains 146 sequences. A sequence listing was filed in the PCT phase having the correct number of sequences; namely 147 sequences total. That sequence listing is now enclosed.

2.3.1. Applicants hereby submit the following:

the Sequence Listing in computer readable form,

complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein;
since this response is being e-filed, the ASCII text file attached hereto should be used as both the paper copy and the CRF, in accordance with EFS practice.

2.3.2. The undersigned attorney or agent hereby states as follows:

(a) this submission does not include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is supported by the specification and does not include new matter [§1.825(a)];

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is identical to that originally filed [§1.825(d)]; and

(e) if reliance is made on a computer readable form presented in a prior application, the paper copy in this application is identical to the CRF in the prior application [§1.821(e)].

2.3.3. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the

relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

2.4. Claim Objections -- We have spelled out the abbreviation LPA in claim 20 (OA §8).

2.5. The objection (OA §9) to claims 40-42, 46 and 47 under 112/4 is moot as these claims are cancelled.

3. Definiteness Issues (OA §§101-4)

The objection to claims 4, 5, 15, 16 and 49 is moot as

these claims are cancelled. Certain claims previously dependent on 15 or 16 have been made dependent on claim 1.

4. Written description (OA §15-17)

The limitation to claims 1 and dependent claims as outlined above drastically reduce the scope of protection, and the 'very broad genus of peptide sequences' has thus been narrowed. Thus, the written description rejection (OA page 11-15) is complied with (the Examiner on page 15 concedes that SEQ ID NOs 1, 2 and 5 meet the written description provision).

Also, as claims 45-49 are cancelled, the WD rejection against these claims is also rendered moot (OA page 15-16).

5. Prior Art Issues (OA §§18-19)

5.1. The examiner concedes that there is allowable subject matter (OA §20). The Examiner in the outstanding OA finds dimeric compounds comprising SEQ ID NO:1 (and the linker) to be obvious over the prior art; while dimeric compounds comprising SEQ ID NO:2 (alone or in combination with another peptide such as SEQ ID NO:1) are deemed allowable. We consider SEQ ID NO:1 as well as SEQ ID NO:2 to be patentable over the prior art.

5.2. Claims 1, 4, 5, 11, 12, 15-17, 20, 21, 35 and 38-49 were rejected as obvious over Kiselyov (WO 03/016351) (IDS #4) in view of Holm (WO 00/18791) (IDS #7). The examiner argues that Kiselyov discloses dimers comprising at least one copy of SEQ ID NO:1, and that it would have been obvious in view of Holm to link the dimers by a linker fo formula (II). Applicant respectfully disagrees.

WO 03/016351 relates to peptide compounds capable of interacting with fibroblast growth factor receptor (FGFR), said compounds comprising a peptide fragment of the first or the second fibronectin type III module of neural cell adhesion molecule (NCAM). WO 03/016351 discloses particular peptide

sequences which are capable of binding to FGFR, among these, e. g. SEQ ID NO: 1 which corresponds to SEQ ID NO: 1 of the present invention.

The preferred compound of WO 03/016351 is a monomer or it comprises monomers independently capable of stimulating FGFR signalling (p.25, lines 17-21). A preferred multimeric compound of WO 03/016351 is a dendrimer comprising four peptide sequences linked to a lysine backbone (p.25, lines 10-12). While it mentions dimers as a less preferred alternative structure, WO 03/016351 does not disclose any particular dimeric compounds comprising SEQ ID NO:1,; i.e. WO 03/016351 does **not specifically** disclose a dimer consisting of two copies of SEQ ID NO:1. Our SEQ ID NO:1 is one of a large number (206) of sequences taught by the reference. Also, it does not teach that the monomeric units of the dimers are linked by a linker (as opposed to a simple bond) let alone a linker of the formula **X[(A)nCOOH][(B)mCOOH]** as required by the present claim. Further, WO 03/016351 nowhere suggests such compounds as advantageous compounds for FGFR binding and treatment FGFR related diseases.

The disclosed compounds are suggested as candidate drugs for treating a number of FGFR related pathological conditions and diseases.

WO 00/18791 describes a method of making peptide compounds comprising two peptide sequences connected to each other through a linker of the formula X[(A)nCOOH][(B)mCOOH]. The method of WO 00/18791 is based on assembly of two identical desired amino acid chains attached to a solid phase by means of achiral dicarboxylic, tricarboxylic or tetracarboxylic acids (p.14, lines 23-26).

WO 00/18791 discusses technical advantages of the disclosed method in relation to methods known in the art (pp.11-15); however, WO 00/18791 does not discuss or present any data showing that a dimeric compound obtained by the method of WO 00/18791 is advantageous in comparison with

either a single presentation of a particular biologically active amino acid sequence or in comparison with another dimeric compound comprising the same particular amino acid sequence obtained by another method.

WO 00/18791 does not relate to the production of a compound capable of binding to FGFR for treatment of FGFR related diseases.

The present invention provides compounds with biological activity related to the dendrimeric FGL peptide (i.e. SEQ ID NO:1) shown in prior art (Cambon et al. (2004) J Neurosci. 17:4197-4204). Purification of the tetramer of the FGL peptide from Cambon et al. has revealed that the product retrieved is highly heterogeneous and therefore not very useful for a pharmaceutical composition.

However, with the provision of the dimeric compounds comprising SEQ ID NO:1 (and 2) according to the present invention, the compounds are much more homogenous; which is of great importance when producing pharmaceuticals (see page 5, line 26 to page 6, line 4 as well as Example 1 and Figure 3 of the present application).

The FGL (SEQ ID NO:1) dimeric peptides of the present application have an improved effect over the individual monomers as cited in WO 03/016351; in that the dimeric FGL (FGLL) produced by the LPA method is more than 200 times more potent than monomeric FGL (FGLm) in promotion of neurite outgrowth (Table 2, page 84 of the present application).

Figure 10 of the present application further shows that other dimers of the FGL peptide such as FGLLys and FGLCys, produced by various other methods known to the skilled person, are functionally inert. Thus, only a dimer produced by the LPA method described in WO 00/18791 retains the activity of said peptide sequences. This surprising finding could not be foreseen from the prior art, as discussed below.

The prior art identified by the Examiner does not provide essential guidance to make functionally active and

pharmaceutically acceptable peptide compounds for the purposes of the present invention. Especially, there is no reference or motivation in Kiselyov WO 03/016351 to make use of the peptide linkers disclosed by Holm WO 00/18791; and vice versa, there is no teaching in Holm WO 00/18791 that the linkers disclosed are particularly useful for the sequence disclosed by Kiselyov WO 03/016351.

A variety of methods for producing peptide dimers or fusion proteins are available to the skilled person, comprising many different types of linkers.

The person skilled in the art would not be able to predict from WO 03/016351 with any kind of certainty that only dimers of SEQ ID NO:1 produced using the linker as defined in claim 1 and WO 00/18791 would have the desired biological effect; while having the required homogeneity required for a pharmaceutical composition. In fact, there is no teaching or motivation in WO 03/016351 to use the linker disclosed in WO 00/18791.

Thus, the surprising finding by the present inventors that only a dimer produced by the LPA method maintains the capability of binding to FGFR, even with an enhanced effect, could not be foreseen from the prior art, and therefore the present invention would not be obvious to the skilled person in view of the combined teachings of WO 03/016351 and WO 00/18791.

It is improper use of hindsight to state that it was obvious that the LPA method would be useful in the present invention. Thus, in view the above arguments it is respectfully submitted that the present invention is

non-obvious over the combination of WO 03/016351 and WO 00/18791.

Respectfully submitted,

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